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Australian Government
Department of Health
Therapeutic Goods Administration

N-nitroso compounds in 'sartan' blood pressure medicines

Information for sponsors

8 November 2019

> **Update: 8 November 2019.** The statement has been updated to clarify the appropriate application types for sponsors making changes to manufacturing processes and/or controls, and to correct a typographical error in the acceptable intakes.

The TGA advises that it is introducing requirements for sponsors of 'sartan' blood pressure medicines to:

- take measures to avoid the presence of *N*-nitroso impurities in their medicines; and
- implement rigorous testing of their medicines to identify the presence of any *N*-nitroso impurities.

These requirements align with those being applied by the European Medicines Agency (EMA). The TGA will provide a 2-year transition period to allow sponsors to review, and if necessary make changes to, their manufacturing processes, and to implement adequate testing methods. The 2-year transition period will be from 13 September 2019 to 13 September 2021.

During the transition period, sponsors must inform the TGA if they identify the presence of *N*-nitroso compounds in their medicines. Changes to manufacturing processes and/or controls, if needed, should be lodged as a 'category 3' request under section 9D(3) of the *Therapeutic Goods Act 1989* (the Act). The TGA will adopt a case by case consideration of any medicines identified as having levels of *N*-nitroso compounds that exceed the acceptable intakes established by the EMA. Medicines that exceed an acceptable intake should not be released for supply, and medicines that are already within the market may be recalled.

What measures do sponsors need to take?

Sponsors in conjunction with their manufacturers should review the manufacturing processes and conduct a risk assessment to determine whether the conditions for *N*-nitroso compound formation are present. Information on the root causes for *N*-nitroso compound formation can be found in the Committee for Medicinal Products for Human Use (CHMP) assessment report - see Useful links.

In particular, the process should be reviewed for the use of nitrite and either secondary or tertiary amines. This includes amines present in solvents or reagents as impurities or degradants. In addition, the process should be reviewed to ensure that the risk of contamination from equipment is eliminated. Where changes to the manufacturing process or controls are required to exclude the presence of *N*-nitroso compounds, sponsors will need to take corrective action, which may require the submission of an appropriate variation request to the TGA.

Sponsors should be aware that investigations into the root causes are ongoing. Currently, risk assessment alone may not be sufficient to mitigate the risk of contamination with *N*-nitroso compounds. Therefore, the TGA is also requiring that sponsors ensure that adequate testing of sartan medicines is in place.

What testing will be required?

Sponsors will be required to implement rigorous testing for the following five *N*-nitroso compounds:

- N-nitrosodimethylamine (**NDMA**)
- N-nitrosodiethylamine (**NDEA**)
- N-nitrosodiisopropylamine (**NDIPA**, also known as DIPNA)
- N-nitrosoethylisopropylamine (**NEIPA**, also known as EIPNA)
- N-Nitroso-N-methyl-4-aminobutyric acid (**NMBA**)

In addition, it is recommended that sponsors test for N-nitrosodibutylamine (**NDBA**), and consider the presence of other *N*-nitroso compounds based on the manufacturing processes.

Testing methods should be sufficiently sensitive to detect levels of *N*-nitroso compounds that would exceed an acceptable intake. At the end of the transition period, it is expected that the validated test methods will have a Limit of Quantitation (LOQ) of no more than 0.03 parts per million (PPM).

Sponsors should refer to testing methods which have been published by international regulatory agencies. For example, the US Food and Drug Administration (FDA) and the European Official Medicines Control Laboratories (OMCL) have published a number of acceptable methods - see Useful links.

Interim acceptable intakes and limits

For a medicine to be considered safe for its intended use, sponsors must ensure that *N*-nitroso compounds are not present at levels above the Acceptable Intake (AI) during the transition period. Following the transition period, sponsors must demonstrate the absence of *N*-nitroso compounds in their medicines. At present, *N*-nitroso compounds are considered to be absent if below the LOQ.

The AI has been derived from animal carcinogenicity studies either for the actual *N*-nitroso compound, or extrapolated from a closely related *N*-nitroso compound. These AI values align with those being used internationally, and have been used to calculate the interim acceptable concentration limits below, based on the Australian Maximum Daily Dose (MDD) of the active pharmaceutical ingredient (API). The limits apply to the API, and may be determined either by testing the API or converting testing results from the finished product back to concentrations in the API.

Active substance	MDD in Australia (mg/day)	Interim acceptable concentration limits (ppm)				
		NDMA*	NMBA*	NDEA**	NDIPA**	NEIPA**
Candesartan	32	3.0	3.0	0.828	0.828	0.828
Irbesartan	300	0.32	0.32	0.088	0.088	0.088
Losartan	100	0.96	0.96	0.265	0.265	0.265
Olmesartan	40	2.4	2.4	0.663	0.663	0.663
Valsartan	320	0.3	0.3	0.083	0.083	0.083

* An AI of 96 ng/day has been used to calculate interim acceptable concentration limits

** An AI of 26.5 ng/day has been used to calculate interim acceptable concentration limits

Further information on the acceptable limits, including methods of determining the AI, can be found on the EMA website - see Useful links.

How will these requirements be implemented?

The TGA will implement these requirements through two administrative mechanisms:

- a condition will be placed on the sponsor's relevant GMP clearance(s); and
- a condition of registration will be applied to sartan medicines using section 28 of the Act.

Specifically, the condition of registration will require sponsors to:

- review the manufacturing process and conduct a risk assessment to determine whether their medicines are at risk of contamination with N-nitroso compound(s);
- implement testing to ensure their medicines do not contain unacceptable levels of *N*-nitroso compound(s), and if testing detects the presence of any *N*-nitroso compound,

this must be investigated to determine the root cause;
    - please note that an unacceptable level of *N*-nitroso compound(s) is considered to be a level above the interim acceptable concentration limit during the 2-year transition period, and a level above the limit of quantitation (0.03 PPM) after the transition period;
- inform the TGA in writing if the risk assessment identifies a risk of contamination that requires corrective action, or if testing identifies the presence of any *N*-nitroso compounds (above the limit of detection).

In addition, sponsors will be required to describe the proposed corrective action(s) that will be implemented to address any identified or potential contamination.

Sponsors should consider whether changes to the manufacturing process and/or controls applied to the API are required to mitigate the formation of *N*-nitroso compounds. For example, sponsors may need to revise the synthetic process, raw material or drug substance specifications and/or in-process controls in order to ensure the quality and safety of their medicine is acceptable.

Sponsors who intend to change the manufacturing process and/or controls to address this issue should make a request to vary the goods under section 9D(3) of the Act (i.e. 'Category 3' request). Note that the notification system cannot be used for this purpose and, in particular, change code ASNT cannot be used in relation to these types of impurities. Sponsors should refer to the Minor variations guidance documents for information relating to the types of changes that require prior approval and for information on how to submit a variation request.

Useful links

Root causes and risk assessment:

How to access a pdf document (//www.tga.gov.au/accessing-documents-website)

***Large file warning:** Attempting to open large files over the Internet within the browser window may cause problems. It is strongly recommended you download this document to your own computer (//www.tga.gov.au/accessing-documents-website#save) and open it from there.

- Committee for Medicinal Products for Human Use (CHMP) Assessment report Referral under Article 31 of Directive 2001/83/EC angiotensin-II-receptor antagonists (sartans) containing a tetrazole group. 14 February 2019. EMA/217823/2019 (pdf,531kb)* (https://www.ema.europa.eu/en/documents/referral/sartans-article-31-referral-chmp-assessment-report_en.pdf)
- NDEA and NDMA limits: 17 April 2019. EMA/248364/2019 (pdf,99kb) (https://www.ema.europa.eu/en/documents/referral/valsartan-article-31-referral-sartan-medicines-companies-review-manufacturing-processes-avoid_en.pdf).
- NDIPA, NEIPA and NMBA limits: 25 June 2019. EMA/351053/2019 (pdf,87kb) (https://www.ema.europa.eu/en/documents/other/temporary-interim-limits-nmba-dipna-eipna-impurities-sartan-blood-pressure-medicines_en.pdf)

Testing methods:

- European Official Medicines Control Laboratories (https://www.edqm.eu/en/ad-hoc-projects-omcl-network) (OMCL)
- FDA test method (https://www.fda.gov/media/125478/download) (Liquid Chromatography-High Resolution Mass Spectrometry method for six nitrosamines)

Minor variations guidance:

- Minor variations to prescription medicines: Process guidance (//www.tga.gov.au/publication/variations-prescription-medicines-excluding-variations-requiring-evaluation-clinical-or-bioequivalence-data-process-guidance)
- Minor variations to prescription medicines, Appendix 1: Variation change types - chemical entities (//www.tga.gov.au/publication/variations-prescription-medicines-excluding-variations-requiring-evaluation-clinical-or-bioequivalence-data-appendix-1-variation-types-chemical-entities)

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